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Remarks

The Office Action mailed October 29, 2003, has been received and reviewed. Claims 1 through 15, 18, 19, and 21 through 32 are pending. Claims 6 through 11, 18, 21 through 26, 29 and 31 have been withdrawn from consideration and are canceled herein without prejudice or disclaimer. Claims 1 through 5, 12 through 15, 19, 27, 28, 30 and 32 stand rejected. The application is to be amended as set forth herein. All amendments and cancellations are made without prejudice or disclaimer. Reconsideration is respectfully requested.

August 5, 2002 Amendment

Applicants note that the Office Action is responsive to the communication filed on March 21, 2002. However, applicants filed an Amendment on August 5, 2002 responsive to the May 20, 2002 Office Action (Paper No. 20). A copy of the Amendment and confirmation postcard is attached hereto as Exhibit 1. Unfortunately, however, the Amendment apparently never reached the Examiner. For the convenience of the Office, applicants have incorporated the content of the August 5, 2002 Amendment herein.

Restriction Requirement

Claims 6 through 11, 18, 21 through 26, 29 and 31 were withdrawn as being drawn to a non-elected invention. In the August 5, 2002 Amendment, applicants proposed to cancel these claims in order to place the application in condition for allowance. Claims 6 through 11, 18, 21 through 26, 29 and 31 are canceled herein without prejudice or disclaimer.

Rejections in view of Cited References

Claims 1 through 5, 12 through 15, 19, 27, 28, 30 and 32 stand rejected under 35 U.S.C. §102(b) as being anticipated by EP0382531 to Gurnett (hereinafter "Gurnett application") or in the alternative under 35 U.S.C. §103(a) to Gurnett. Claims 14 and 28 also stand rejected under 35 U.S.C. §103(a) as being unpatentable under EP0382531 to Gurnett, U.S. Patent 4,981,684 to MacKenzie et al. and U.S. Patent 5,597,807 to Estrada et al. Claim 12 has been canceled and incorporated into claim 1, thus the rejection of claim 12 is moot. Applicants respectfully traverse the rejections.

Claims 1-5, 13-15, 19, and 32 have been amended herein and include no new matter. The elements of canceled claim 12 have been incorporated into claim 1. Further, basis for the "native form" element can be found throughout the as-filed specification, for example, pages 23-24.

The Gurnett application fails to disclose, either expressly or inherently, "a vaccine composition comprising at least one protein or antigenic fragment and a pharmaceutically acceptable carrier, wherein said at least one protein or antigenic fragment in its native form: (a) is present in the hydrophilic phase of a tertoctylphenoxypoly (ethoxyethanol) extract of *Eimeria* sporozoites; and (b) has a molecular mass of about 26-30 kDa as determined by SDS-PAGE under reducing conditions" as recited in claim 1 of the presently claimed invention, the immunological reagent of claim 19, the test kit of claim 30, or the method of making a vaccine composition of claim 32.

The Gurnett application discloses glycolipid linked membrane associated proteins that have a glycolipid anchor with which they are bound to the outer *Eimeria* surface-membrane. This anchor can be cut with a lipase from *Trypanosoma brucei* which releases these proteins in soluble form. After release, these proteins in their soluble form can be bound by anti-CRD antibody, which "reacts specifically with the carbohydrate portion of the VSG glycolipid anchor" (The Gurnett application, page 5, line 22) and was raised against Trypanosoma sVSG. This is consistent with the observed staining and agglutination of the *Eimeria* sporozoite outer membrane after binding with anti-TX114B antibody (which is directed against "coccidial proteins found in the TX114B detergent phase"; the Gurnett application, page 5, line 54).

An article by Gurnett, "A Family of Glycolipid Linked Proteins in *Eiemria tenella*", *Mol. and Biochem. Parasitology* (1990) is submitted herewith (hereinafter "the Gurnett article"). The Gurnett article lacks any discussion of vaccines and only discloses an antiserum against the detergent phase proteins (hydrophobic proteins), the TX114B antiserum. (Gurnett article, page 179, left column)

Example 12 of the Gurnett application discloses the details of a vaccination in which an HPLC isolated hydrophobic 26kDa protein from *E. tenella* sporozoites is tested in a vaccination challenge in chickens. (the Gurnett application, page 14, line 30- page 15, line 5). The 26kDa protein used in the vaccination is one of the proteins listed in Table 2 (The Gurnett application, page 12). The proteins in Table 2 were isolated from the (hydrophobic) TX114B fraction by HPLC (Example 8) and identified by Western blot using anti-CRD antibody (Example 9), where

binding of the antibody required lipase treatment first (apparently the epitope recognized by the anti-CRD antibody otherwise is hidden, *i.e.*, cryptic). Polyclonal rabbit sera were produced against these proteins (Example 10). Some of the proteins were subjected to protein sequencing (Example 11), but only the 26kDa protein was used in the vaccination trial (Example 12). In the examples, the proteins are consistently described as "glycolipid linked". Thus, the Gurnett application lacks any disclosure of using proteins that are not glycolipid linked, or not hydrophobic, in a vaccine.

As the Gurnett application fails to disclose, either expressly or inherently, a vaccine composition comprising at least one protein or antigenic fragment and a pharmaceutically acceptable carrier, wherein said at least one protein or antigenic fragment in its native form is present in the hydrophilic phase of a tertoctylphenoxypoly (ethoxyethanol) extract of *Eimeria* sporozoites, it cannot anticipate claim 1 of the presently claimed invention.

Claims 2-5 and 13-15 depend from claim 1 and are distinguished from Gurnett at least for the same reasons as claim 1. Similarly, the Gurnett application fails to disclose, either expressly or inherently, the immunological reagent of claim 19, the test kit for the diagnosis of *Eimeria* infection of claim 30, or a method of making a vaccine composition of claim 32. Accordingly, these claims cannot be anticipated by the Gurnett application.

The presently claimed invention is not rendered obvious by the Gurnett application. First, the Gurnett application fails to teach or suggest a vaccine composition comprising at least one protein or antigenic fragment and a pharmaceutically acceptable carrier (or an immunological reagent, test kit or method of making a vaccine), wherein said at least one protein or antigenic fragment in its native form is present in the hydrophilic phase of a tertoctylphenoxypoly (ethoxyethanol) extract of *Eimeria* sporozoites. Second, no motivation exists in the Gurnett application to use the hydrophilic Eimeria proteins in a vaccination, as an immunological reagent or in a test kit.

The Gurnett application discloses the immunogenicity of a 26kDa protein that is hydrophobic in its native form and is only rendered hydrophilic upon lipase treatment. the Gurnett application fails to teach or suggest a vaccination (immunological reagent or test kit) comprising at least one protein or antigenic fragment *that in its native form* is present in the hydrophilic phase of a tertoctylphenoxypoly (ethoxyethanol) extract of *Eimeria* sporozoites. The proteins from the detergent (hydrophobic) fraction of the Gurnett application are recognized by

TX114B antiserum in Western blot which only establishes the antigenicity of the hydrophobic proteins which is not equivalent to immunogenicity. The TX114 extracts were made of the sporozoite lysate, either before or after lipase treatment (the Gurnett application Example 10, page 13, lines 12-13). These fractions were incubated with the specific polyclonal antisera. Again, this does not teach or suggest immunogenicity of Eimeria sporozoite proteins that were made hydrophilic by lipase treatment, but rather antigenicity.

Example 12 of the Gurnett application provides the only disclosure of immunoprotectivity. But, Example 12 is directed to the 26kDa protein isolated from the hydrophobic fraction and was not lipase treated prior to generation of the vaccine. While, the Gurnett application includes a description of a lipase treated 26kDa protein for the treatment of the protein blotted on nitrocellulose in Example 8, in order to allow CRD antiserum to bind to its cryptic epitope. However, this is not an enabling disclosure of the vaccine composition, the immunological reagent, test kit or method of the presently claimed invention.

The Gurnett application discloses lipase digestion of hydrophobic proteins only to determine membrane linkage, to test similarity of Eimeria proteins to VSG proteins, and to open up the cryptic epitope for the CRD antiserum. The Gurnett application fails to teach or suggest incorporating a protein that is hydrophilic in its native form in a vaccine, use of such a protein as an immunological reagent or in a test kit. Further, the Gurnett application lacks any disclosure to enable one skilled in the art to make a vaccine incorporating a protein that is hydrophilic in its native form by modifying an immunogenic hydrophobic protein through lipase treatment. The Gurnett application lacks any disclosure that the proteins in the hydrophilic phase of the extracts are immunoprotective.

Accordingly, claims 1-5, 13-15, 19, 27, 28, 30 and 32 are distinguished over the reference.

Claims 14 and 28 depend from claim 1 and avoid the prior art, at least, for substantially the same reasons. For the reasons stated herein, the Gurnett application fails to teach or suggest the vaccine including the hydrophilic protein of the presently claimed invention. Neither Mackenzie nor Estrada teaches or suggests the utility of the hydrophilic Eimeria sporozoite proteins of the invention as vaccines. Therefore, the proposed combination of references fails to teach or suggest such vaccines either with Quil A or in unit dosage form. Reconsideration and withdrawal of the rejection is requested.

Conclusion

In view of the amendments and remarks presented herein, applicants respectfully submit that claims 1-5, 13-15, 19, 27, 28, 30 and 32, are allowable, and an early notice thereof is respectfully solicited. If questions should remain after consideration of the foregoing, the Examiner is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,

Krista Weber Powell
Registration No. 47,867
Attorney for Applicants
TRASK BRITT, PC
P. O. Box 2550
Salt Lake City, Utah 84110-2550
Telephone: (801) 532-1922

Date: May 25, 2004
Enclosure: August 5, 2002 Amendment

THE PATENT & TRADEMARK OFFICE MAILROOM DATE STAMPED HEREON IS AN ACKNOWLEDGEMENT THAT ON THIS DATE THE PATENT & TRADEMARK OFFICE RECEIVED:

Amendment under 37 CFR 1.116 (6 pages); and Exhibit 1 (6 pages).

Invention:	VACCINES AGAINST EIMERIA MEDIATED DISORDERS
Applicant(s):	Vermeulen et al.
Filing Date:	April 8, 1998
Serial No.:	09/056,806
Date Sent:	August 5, 2002 via Express Mail Label No. EL740515989US
Docket No.:	1963-5106US
ACT/le	

TRASKBRITT
P.O. Box 2550
Salt Lake City, UT 84110-2550

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Vermeulen et al.

Serial No.: 09/056,806

Filed: April 8, 1998

For: VACCINES AGAINST EIMERIA MEDIATED DISORDERS

Examiner: S. Turner, Ph.D.

Group Art Unit: 1647

Attorney Docket No.: 5106US

NOTICE OF EXPRESS MAILING

Express Mail Mailing Label Number: EL740515989US

Date of Deposit with USPS: August 5, 2002

Person making Deposit: Jon Wentz

AMENDMENT UNDER 37 CFR 1.116
EXPEDITED PROCEDURE - EXAMINING GROUP 1647

Box AF
Commissioner for Patents
Washington, D.C. 20231

Sir:

Responsive to the Office Action mailed May 20, 2002, please amend the referenced application as follows:

IN THE CLAIMS:

Please cancel claims 6 through 11, 18, 21 through 26, 29 and 31 without prejudice or disclaimer.

1. (Amended six times) A composition free of whole *Eimeria* parasites, which comprises at least one protein or antigenic fragment thereof, wherein said protein:

(a) is present in the hydrophilic phase of a tertoctylphenoxypoly (ethoxyethanol) extract of total *Eimeria* sporozoites; and

(b) has a molecular mass of about 26-30 kDa as determined by SDS-PAGE under reducing conditions.

Remarks

The Office Action mailed 20 May 2002, has been received and reviewed. Claims 1 through 15, 18, 19, and 21 through 32 are pending. Claims 6 through 11, 18, 21 through 26, 29 and 31 have been withdrawn from consideration and are canceled herein without prejudice or disclaimer. Claims 1 through 5, 12 through 15, 19, 27, 28, 30 and 32 stand rejected. The application is proposed to be amended as set forth herein. All amendments and cancellations are made without prejudice or disclaimer. Reconsideration is respectfully requested.

March 21, 2002 Supplemental Amendment

Applicants note that the Office Action is responsive to the communication filed on February 21, 2002. However, applicants filed a Supplemental Amendment on March 21, 2002. A copy of the Supplemental Amendment and confirmation of transmission is attached hereto as Exhibit 1. Unfortunately, however, the Supplemental Amendment apparently never made it to the Examiner. For the convenience of the Office, applicants have incorporated the content of the March 21, 2002 Supplemental Amendment herein.

Restriction Requirement

Claims 6 through 11, 18, 21 through 26, 29 and 31 were withdrawn as being drawn to a non-elected invention. Applicants have accordingly canceled these claims in order to place the application in condition for allowance.

Interview

Applicants wish to thank the Examiner for the courtesy extended during the personal interview conducted March 21, 2002. The applicants found this interview especially productive as evidenced by the Interview Summary (Paper No. 19),

> Applicants proposed amendment would appear to overcome the rejections of record. However, the newly proposed claim will require further search and consideration to determine patentability.

(Paper No. 19).

Rejections in view of Cited References

Claims 1 through 5, 12 through 15, 19, 27, 28, 30 and 32 stand rejected under 35 U.S.C. §102(b) as being anticipated by EP0382531 to Gurnett. Claims 14 and 28 also stand rejected under 35 U.S.C. §103(a) as being unpatentable under EP0382531 to Gurnett, U.S. Patent 4,981,684 to MacKenzie et al. and U.S. Patent 5,597,807 to Estrada et al. Applicants respectfully traverse the rejections.

Applicants' propose amended claim 1 recites a protein present "in the hydrophilic phase of a tertoctylphenoxypoly (ethoxyethanol) extract of total *Eimeria* sporozoites". Support for the amendment can be found in the specification, for example, on page 23, lines 12 through the end. As discussed at the Interview and confirmed in the Interview Summary, the proposed amendment more clearly defines the invention and distinguishes over the prior art of record.

As agreed at the interview, the primary reference, Gurnett, does not disclose comprising a protein present in the hydrophilic phase of a tertoctylphenoxypoly (ethoxyethanol) extract of **total** *Eimeria* sporozoites. Gurnett teaches first reacting the sporozoites with a lipase, then conducting a phase separation including. Accordingly, claim 1 distinguishes over the reference. Claims 14 and 28 depend from claim 1 and avoid the prior art, at least, for substantially the same reasons.

Applicants submit that the proposed amendment to claim 1 should be entered because the amendment is supported by the as-filed specification and drawings and do not add any new matter to the application. Also, applicants tried to earlier submit it, but, evidently, the fax did not make it to the Examiner through no fault of applicants. Further, the amendments do not raise new issues or require a further search. Finally, if the Examiner determines that the amendment does not place the application in condition for allowance, entry is respectfully requested upon filing of a Notice of Appeal herein. Reconsideration of the rejection is requested.

Conclusion

In view of the amendments and remarks presented herein, applicants respectfully submit that claims 1-5, 12-15, 19, 27, 28, 30 and 32, are allowable, and an early notice thereof is respectfully solicited. If questions should remain after consideration of the foregoing, the Examiner is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,

Allen C. Turner
Registration No. 33,041
Attorney for Applicants
TRASK BRITT, PC
P. O. Box 2550
Salt Lake City, Utah 84110-2550
Telephone: (801) 532-1922

Date: August 4, 2002
Attachment: Marked up version of the amended claims

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended six times) A composition free of whole *Eimeria* parasites, which comprises [one or more proteins, or fragments] at least one protein or antigenic fragment thereof, wherein said protein [proteins]:

(a) [are] is present in the hydrophilic phase of a tertoctylphenoxypoly (ethoxyethanol) extract of total *Eimeria* sporozoites; and

(b) [have] has a molecular mass [masses] of about 26-30 kDa [± 5 kDa when] as determined by SDS-PAGE under reducing conditions[;

and wherein said composition consists essentially of proteins which are non-membrane-bound in *Eimeria]*.